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Abstract: An 11-year-old, 41-kg female spayed mixed-breed dog was examined for a chronic left hind limb lameness, with swelling of the proximal left tibia. A tibial plateau leveling osteotomy (TPLO) using an angle stable implant had been performed 8 years earlier at the site. Initial radiography showed mild degenerative signs in the stifle joint and osteolytic lesions in the proximal tibial metaphysis. Three weeks later, the clinical and radiographic changes had worsened. A transition from a moth-eaten pattern to permeative bone lysis was radiographically evident, along with an extensive increase of soft tissue swelling. Ultrasonographically-guided fine needle aspiration of the epiperiosteal tissue and lymph nodes, CT with pre-and post-contrast scans, and an incisional biopsy were performed. The radiographic and CT findings were consistent with an aggressive and monostotic bone lesion at the site of previous TPLO. The cytology and histology confirmed the diagnosis of an osteosarcoma (OSA) with a chondroid differentiation. Three months after a palliative hind limb amputation, the dog was euthanased. CONCLUSION We believe that this is the first report of implant-related OSA at the site of a previous TPLO with a new generation angle stable implant

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Osteosarcoma 8 years after tibial plateau leveling osteotomy with an angle stable implant in a dog

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CASE REPORT An 11-year-old, 41-kg female spayed mixed-breed dog was examined for a chronic left hind limb lameness, with swelling of the proximal left tibia. A tibial plateau leveling osteotomy (TPLO) using an angle stable implant had been performed 8 years earlier at the site. Initial radiography showed mild degenerative signs in the stifle joint and osteolytic lesions in the proximal tibial metaphysis. Three weeks later, the clinical and radiographic changes had worsened. A transition from a moth-eaten pattern to permeative bone lysis was radiographically evident, along with an extensive increase of soft tissue swelling. Ultrasonographically-guided fine needle aspiration of the epiperiostial tissue and lymph nodes, CT with pre- and post-contrast scans, and an incisional biopsy were performed. The radiographic and CT findings were consistent with an aggressive and monostotic bone lesion at the site of previous TPLO. The cytology and histology confirmed the diagnosis of an osteosarcoma (OSA) with a chondroid differentiation. Three months after a palliative hind limb amputation, the dog was euthanased.

CONCLUSION We believe that this is the first report of implant-related OSA at the site of a previous TPLO with a new generation angle stable implant.

KEYWORDS osteosarcoma, tibial plateau leveling osteotomy

ABBREVIATIONS CT, computed tomography; DJD, degenerative joint disease; OSA,

osteosarcoma; TPLO, tibial plateau leveling osteotomy

Osteosarcoma (OSA) is a highly aggressive, locally invasive, mesenchymal (spindle cell) tumor which occurs most frequently in the metaphysis of the long tubular bones such as the radius, humerus, femur and proximal tibia.[1] It is the most common primary bone tumor in dogs, accounting for 85% of malignancies of the skeleton.[1] The aetiology of OSA is likely multifactorial. Morphogenic parameters such as weight and height of the dog are well-known risk factors. Other risk factors include diseases that may cause local chronic reaction in the bone structure such as osteomyelitis, osteochondrosis, previous fracture and use of metallic implants for fracture fixation.[1,2] OSA has been reported in dogs after fracture repair[2,3] and in elective surgeries such as total hip replacement,[4] tibial tuberosity advancement[5] and tibial plateau leveling osteotomy (TPLO).[6-10] OSA at the site of TPLO have been reported with the use of stainless steel plates from Slocum Enterprises (Eugene, Oregon, USA), DePuy Synthes Vet (West Chester, PA, USA) and Veterinary Instrumentation (Sheffield, England).[3,7,10,11] To the authors' knowledge, the present report is the first relating to an OSA at the site of a conical coupling angle stable TPLO plate (Fixin, Intrauma, Rivoli, Italy).

CASE REPORT

An 11-year-old, 41-kg, female spayed mixed-breed dog presented for a chronic (more than 1 month) left hind limb lameness associated with increasing reluctance to exercise and mild inappetence. There was no history of trauma at that time. The dog had been treated 8 years earlier for left cranial cruciate ligament rupture with a TPLO using an angle stable implant (3.0-3.5 TPLO plate; Fixin). The plate was removed after 4 years, due to a skin fistula close to the implant site and painful palpation of the medial tibia. Cytology of the discharge revealed mild neutrophilic inflammation with no signs of cellular atypia. Empirical antibiotic therapy (Cefazolin, 25 mg/kg per os SID; Cefazolina Teva 1 g, Teva Italia SRL, Milano, Italy) was administered for 20 days and the dog made a clinical recovery.

On orthopaedic examination at presentation, the dog was moderately active, with a grade 2/4 left hind limb lameness. Clinical examination, including mucous membrane colour and refill, thoracic auscultation, cardiorespiratory parameters, abdominal palpation and rectal temperature, were

unremarkable. A mild soft tissue swelling was detected at the level of the left medial proximal tibial metaphysis, with pain on palpation and reduced stifle flexion (70°).

Orthogonal view radiographs of the left stifle showed diffuse, moderately irregular, radiolucent areas (a 'moth-eaten pattern') in the metaphyseal region of the left proximal tibia (Figure 1A and B), suggesting bone lysis. Poorly defined transition zones were observed in the tibial metaphysis, except for a proximal osteolytic lesion that was surrounded by a wide sclerotic reaction (Figure 1A). Signs of a multilayered periosteal reaction were noted in the medial tibial cortex (Figure 1A and B).

Oral treatment with carprofen (Rimadyl 100 mg; Zoetis, Parsippany, NJ, USA; 4 mg/kg SID for 14 days) and tramadol (Altadol, 50 mg/ml; Formevet SRL, Milano, Italy; 3 mg/kg TID for 3 days) were prescribed.

At the 3-week revisit, the degree of lameness (3/4) and the amount of swelling in the proximal left tibia had increased. A second series of left stifle radiographs were taken and showed a rapid worsening of the radiographic signs (Figure 1C and D). The osteolytic pattern was becoming permeative with areas of cortical destruction at the caudolateral aspect of the proximal tibial metaphysis (*tibialis cranialis* fossa). The multilayered periosteal reaction had increased, and new periosteal bone formation of the tibial crest was detected (Figure 1C). Signs of degenerative joint disease (DJD) were also observed on the patella, trochlear ridges, tibial plateau and at the insertion of the patellar tendon. An intraarticular radiopaque body was also noticed, which was considered to be compatible with DJD, neoplasia or meniscal mineralisation. These radiographic findings were considered to be most consistent with an aggressive and monostotic bone lesion at the site of the previous TPLO. Differential diagnoses included: other neoplasia (primary or metastatic), and osteomyelitis (fungal bone infection). Additionally, a radiographic diagnosis of DJD of the left stifle was made.

Further diagnostic examinations were performed, due to the rapid progression of radiographic findings, persistence of lameness and lack of response to medical therapy. An ultrasonographically-guided fine needle aspiration of the epiperiosteal and bone tissue, and of the inguinal, internal iliac

and popliteal lymph nodes were performed. Subsequently, a whole body computed tomography (CT) examination with pre- and post-contrast scans was done as part of complete staging tests. An open incisional biopsy of the lesion on the proximal left tibia and removal of the popliteal lymph node were also undertaken.

The CT scans confirmed the presence of the proximal left tibial osteolytic lesions associated with medullar sclerosis and swelling and irregularity of peripheral soft tissues (Figure 2). No intraarticular involvement was noted. A neovascularization process was observed in the post-contrast scans. Multiple collateral vessels in the popliteal notch arising from the popliteal artery were visible (Figure 2). Post-contrast hyper-attenuation of the ipsilateral popliteal, medial inguinal and hypogastric lymph nodes were also found. Additionally, bilateral nodular lung degeneration was noticed. The bone lesions were consistent with aggressive metastatic neoplasia, most likely a malignant mesenchymal tumor. The primary differential diagnosis for the pulmonary lesions was multifocal metastatic disease, with granulomas or inflammatory foci unlikely possibilities. Radiographs performed after the biopsy (Figure 3) revealed increased cortical lysis, loss of the trabecular pattern on the tibial metaphysis and an extensive increase of soft tissue swelling in the proximal tibial metaphysis (‘sunburst’ periosteal reaction).

The cytological slides of the epiperiosteal and tibial tissues were characterised by low cellularity and good preservation. A single cell population comprised medium-sized, round or irregularly shaped cells with indistinct borders. These cells had abundant, clear or slightly basophilic, cytoplasm with the presence of vacuoles (Figure 4). Most cells had a single, round, eccentrically located nucleus, with finely granular chromatin and a single nucleolus. Binucleated cells were occasionally present. Anisocytosis and anisokaryosis were moderate. Based on cytological features, a mesenchymal (spindle cell) neoplasm was diagnosed.

Histopathology of epiperiosteal and tibial samples revealed atypical cellular proliferation with an extensive osteoid or chondroid matrix, compatible with an OSA with chondroid differentiation.

The dog underwent a palliative left hind limb amputation to provide pain relief. The owner elected not to proceed with post-surgical chemotherapy. Three months later, the dog became anorectic and reluctant to walk and was euthanased. No necropsy was allowed by the owner.

DISCUSSION

OSA was the most likely differential diagnosis, due to monostotic and metaphyseal location of osteolytic bone lesions, periosteal reactions and surrounding soft tissue alterations. The radiographic and tomographic signs, together with the cytological and histological results, confirmed the diagnosis. Lameness, swelling and pain at the site of the tumour are some of the commonest clinical signs for OSA.[1] The pain is often caused by disruption or microfractures of the periosteal tissue induced by osteolysis of cortical bone.[1]

The CT scan, while not essential to confirm the diagnosis, was performed to document changes consistent with metastases in other bones, lungs, lymph nodes or other tissues. CT can detect soft tissue dense nodules that are not visible with radiographs until they reach 6-8 mm size.[1]

Pulmonary metastases of OSA are very common,[12] with 90% of patients who only received palliative amputation reported to die from such metastases.[13] OSA that metastasises either locally or regionally, regardless of its histological grade, is classified as stage III.[1,12] Reported mean survival time of dogs with stage III OSA treated with only a palliative amputation ranged from 3 days[12] to 5-6 months.[13] Median survival time of dogs treated with amputation and chemotherapy was found to be 76 days[12] and 313 days.[10] Median survival time with the combination of amputation, radiotherapy and chemotherapy was 136 days.[12] The survival time of our patient, which was treated with only a palliative amputation, was 97 days after the surgery.

The reported median time to occurrence or diagnosis of OSA at a TPLO site ranges approximately from 4 to 6.5 years.[7,8,10,14] In the present case, the time of diagnosis of OSA was 8.3 years after the TPLO.

In human medicine, the development of implant-associated OSA is a sporadically reported event.[15,16] In veterinary medicine, OSA has been reported in dogs following fracture treatment[3] and elective surgeries, such as TPLO.[4,5,7-11,14] One of the latter TPLO papers reported a low incidence of OSA, finding only 11 cases out of a total of 2,464 TPLO.[14] Nevertheless, two of the publications,[7,14] noted that the same stainless steel plate was used to perform the surgery (TPLO bone plate, Slocum Enterprises). Therefore, questions were raised about a potential correlation between implant composition and development of OSA. Two studies[7,17] found remarkable corrosion on the TPLO implant in cases with a diagnosis of OSA. However, a cause-and-effect relationship between such corrosion and development of OSA was not clearly evident. Nevertheless, dogs that have undergone a TPLO have been reported to be 40 as likely to develop an OSA of the proximal tibia than dogs who have not undergone the procedure.[11]

Another study analysed the metallurgic composition of the Slocum implant to investigate implant-related risk factors.[18] An inhomogeneous structure with variations of chemical composition was found not only between implants, but also between regions of the same plate.[18] However, the latter findings were challenged in another publication[19] that reported neither topographic nor chemical micro-changes in TPLO plates implanted for up to 54 months. Finally, a recent study reported a release of metal ions from Slocum implants.[20] According to the latter authors, this was caused by implant corrosion and may have been the neoplastic stimulus for cells adjacent to the implant.[20]

To the authors' knowledge, the present case is the first report of OSA at a TPLO site where a

new generation conical coupling angle stable plate was used. The implant also is made of stainless steel (AISI 316LVM), while the screws and bushing-inserts are composed of titanium alloy (Ti-6Al-4V).[21] The locking implant configuration is designed to minimise the bone-plate interface and better preserve the periosteum and extraosseous vascularisation. These implants has been also successfully applied in a supercutaneous fashion to minimise the iatrogenic damage to the vascular periosseous structures.[22,23] The augmented bone to plate interface, theoretically decreases the risks of corrosion-related osteolysis under the plate. We did not perform any material analysis on the implant after its removal but noted no visible structural abnormalities at the time. Consequently, while we can speculate that the implant may have triggered tumourogenesis, as has been suggested with other types of TPLO plates, it is important to remember that the proximal tibial epiphyses is a common site for spontaneous bone neoplasia, accounting for 5-7% of all naturally occurring canine tumours.[7]

In conclusion, OSA may be a catastrophic event years after TPLO. Its relationship, if any, to the implant itself is unclear. The fact that such OSA have arisen after the use of several different plates, sometimes with and sometimes without evidence of corrosion, supports the thesis that the pathophysiology of tumourogenesis may be related more to chronic irritation at the site.

Conflict of interest

I disclose that none of the authors involved have financial benefits from this pa

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Figure legends

Fig 1: Orthogonal radiographic study performed on a 11 years-old 41 kg spayed female mixed-breed dog, evaluated after a history of a left hind limb lameness with swelling in the proximal tibia. Mediolateral and craniocaudal views of the left stifle taken at the initial examination (A,B) and after 3 weeks (C,D). There is evidence of osteolytic bone lesions with a moth-eaten pattern in the proximal tibial metaphysis (arrows) associated with the presence of a poorly defined transition zone. However, a wide sclerosis reaction was found in the proximal area of tibial metaphysis (asterix). Mild signs of a periosteal reaction in were visible in the medial tibial cortex (B) and possibly compatible with the previous presence of the TPLO plate. After 3 weeks, a periosteal neoformation was found at the level of the cranial tibial crest (dotted arrows) along with areas with cortical lysis (star) and increased epiperiosteal soft tissue swelling (dotted line). Signs of degenerative joint disease were diffusely observable (circle).

Fig 2: Computed tomographic (CT) post contrast 3D rendered view of the pelvis and hind limbs. A muscular filter was used to identify the muscular planes affected by the soft tissue swelling of the left hind limb. A medial and lateral soft tissue enlargement was evident (A). Lateral and medial view of the left hind limb (B). The left femoral artery with their distal ramifications were visible (B). On the caudal view (C), a vessel filter was selected to evaluate the neovascularization of the suspected mass. Substantial differences relative to distal ramifications of the popliteal artery and collateral vessels neoformation were found between the pathological (left) and normal hind limb (right).

Fig 3: Mediolateral (A) and caudocranial (B) radiographic views of the left stifle taken six weeks after the first examination. The trabecular pattern of the tibial metaphysis was altered due to an increase of bone osteolytic lesions (asterix) and the mass extension into the soft tissue (dotted line), now visible also in the caudal area of the popliteal notch (A). An increased cortical lysis was visible (star).

Fig 4: Cytological views of an ultrasonographically-guided fine needle aspiration (FNA) of the tibial tissue. The presence of several vacuoles in the cytoplasm along with the presence of an eccentrically positioned nucleus were found (asterix). Binucleated cells were occasionally observable (arrow).